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REMARKS

The amendments made to the claims herein are made to clarify the nature of the invention and to set forth specific embodiments of the invention. No new matter is introduced into the application by means of these amendments. Support for the specific dosage ranges can be found on pages 20-21 of the application.

Claims 20-25 and 61 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that although the specification is enabling for a method of increasing or maintaining the plasma or serum levels of cadmium in a human whose levels are lower than the normal range it is not enabling for decreasing cadmium levels in a human whose levels are greater than normal. Applicant respectfully submits that this rejection with regard to claims 20-25 has been obviated by the amendments to claims 20, 21 and 22. Applicant also respectfully submits that the rejection of claim 61 was in error as the original (and current) language of claim 61 is directed to a method of correcting a cadmium deficiency.

Claims 20-22, 24-25 and 61 were rejected under 35 U.S.C. § 112, second paragraph, on the basis that the recitations "balance," "said unbalanced levels" and "sufficient to balance said cadmium concentration" rendered the claims indefinite.

Applicant respectfully submits that the rejection as applied to claims 20-22 and 24-25 has been obviated by the amendments to claims 20, 21 and 22. Again, Applicant also respectfully submits that this rejection as applied to independent claim 61 was in error as the claim does not contain any of the language on which the rejection was based.

Claims 20, 23-24 and 61 have been rejected under 35 U.S.C. §102(b) as anticipated by Jacobson et al. The examiner asserted that Jacobson et al. disclose the administration of 20 trace elements, including cadmium, to humans to correct negative balances of the elements. The examiner further asserted that the amounts of cadmium administered daily were 50-60 µg (0.05-0.06 mg) or 5-68 µg, which was within the instantly claimed range. This rejection is traversed.

The presently claimed invention is directed to a method of treating a person suffering from deficient levels of cadmium in his body fluids and tissues by administering to the person a series of daily doses of cadmium at dose levels of about 0.025 mg to about 2 mg per day (equivalent to a dose level of about 25 - 2000 µg per day). This invention is not taught or suggested by Jacobson et al.

Jacobson et al. report a 5 day study in which they administered a number of trace elements parenterally to four

adult human males. The amount of cadmium administered ranged from 1.2 to 4.0 µg per day. See Table 5, page 114. This dosage amount is far below the amount of cadmium to be administered in accordance with the present invention. The present claims require a concentration of 0.025 - 2 mg be administered, which is the equivalent of 25-2000 µg. The amounts of cadmium administered in the Jacobson study was so small that three of the four patients excreted higher amounts of cadmium in their urine than were administered.

The examiner's statement that the paper teaches the administration of 0.05-0.06 mg of cadmium is a mis-reading of the reference. The passage the examiner cited from page 121 does not relate to the amount of cadmium parenterally administered to the subjects in this study. Rather, the reference to 0.05 - 0.06 mg of cadmium is a reference to the average amount of cadmium typically ingested per day as part of one's typical food intake; the authors then note that the food in ordinary hospital diets provide from 0.005 - 0.068 mg of cadmium daily. Applicant notes in the background of his application that small amounts of cadmium are ingested as a matter of course in various foods and then teaches that oftentimes, especially for those who consume typical Western diets, the amounts ingested are insufficient, such that cadmium must actually be administered to humans to

minimize or eliminate the cadmium deficiency that has developed as a result of the inadequate intake of cadmium in food. Applicants teach the administration of cadmium, supplemental to that typically obtained in food, to prevent or treat cadmium deficiencies in body fluids and tissues.

The cited reference is deficient in that there is no indication that the four men to whom the parenteral nutritional supplement was administered suffered from a cadmium deficiency. Even if they did, the amounts of cadmium given them, from 0.0012 µg - 0.004 mg, was far less than the amount required by the pending claims and would not be sufficient to treat a cadmium deficiency, which, as indicated in the present application, can be at least 15% below normal physiological levels. Jacobson et al. certainly do not teach or suggest that greater amounts could or should be given. The largest amount of cadmium they administered, 0.004 mg, is only <u>one-sixth</u> the minimum amount taught and claimed by the Applicant. Moreover, there is no indication in the Jacobson et al. paper that the authors are advocating the administration of cadmium; the discussion of dietary cadmium is part of a larger discussion of trace elements not established as essential for man or animals, and they note that cadmium "has not been attributed any special role in the living cell." Indeed, the very small amounts of cadmium

administered appear to have been present unintentionally. Table 1 of the paper provides the composition of the parenteral nutrition solutions administered during the study. Different solutions were administered at different times of the day. The solutions were (1) a carbohydrate solution and a soluble vitamin mixture, (2) an amino acid solution and an electrolyte solution, (3) a combination of a fat emulsion, lipovit emulsion and heparin, and (4) a carbohydrate solution. The components of the different solutions are listed in subsequent tables, none of which include cadmium as a component. In the Abstract, the authors note that the "intended intravenous supply of trace elements [presumably those listed in the initial tables of the paper] corresponded approximately to the analyzed supply," but that "all other trace elements determined were found to be unintentionally administered in small amounts."

At the end of their paper the authors discuss recommendations for trace element dosage, per 24 hours, in total parenteral nutrition for adults. None of the recommendations, provided in Table 6, include cadmium as an element to be administered. The authors state that the US National Research Council recommended that only iodine, iron and zinc be included regularly in the diet and that other trace elements are supposed to be adequate in the variety of common foods eaten. The authors

suggest that on the basis of their results, trace element solutions used in total parenteral nutrition might be improved if they provided more zinc and less iron, to cover the basic requirements more appropriately. "Otherwise, the quantities of infusion solutions used in the total parenteral nutrition studied seem to supply adequate basic amounts of trace elements, essential for human nutrition" (from the paragraph bridging pages 124-125). From this discussion, one would be left believing that, at best, cadmium should be administered only at doses not to exceed 4 µg, and that perhaps cadmium need not be administered at all. There is no realization that persons can suffer from a cadmium deficiency or that relatively large amounts of cadmium can or should be administered to such people to treat such deficiencies. Certainly, if, indeed, any of the patients in the study had a cadmium deficiency, they did not receive treatment for that deficiency.

In view of the deficiencies of the Jacobson et al. reference, the reference does not anticipate the claims of this application.

Claims 20 and 61 have been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent 4,225,592, issued to Lakatos. The examiner asserted that the '592 patent teaches that trace elements, including cadmium, are well-known to be administered to

a human as nutrition, citing column 9, lines 25-46. She noted that the teachings regarding the administration of these trace elements have been cited from several earlier prior art references (col. 9, lines 21-46). This rejection is traversed.

The focus of the '592 patent, the administration of complexes of oligo- and polygalacturonic acid formed with selected essential metal ions, none of which is cadmium, is of no relevance to the presently claimed invention, and the examiner has not claimed otherwise. The examiner's focus on this reference is on a discussion of trace elements in column 9 of the patent. As noted above, the examiner has asserted that the paragraph extending from lines 21-46 of this column teach that it is well-known to administer cadmium and other trace elements to humans as nutrition. Applicant respectfully submits that the examiner has mis-read the discussion in the cited paragraph. What the paragraph actually provides is that the absorption of magnesium and trace metals such as iron, zinc and copper and chromium significantly decreases and their secretion increases with age, and that as a result, disorders such as anemia, athero- and arteriosclerosis, diabetes, cardiovascular diseases, nephrolithiasis and ulcus emerge. The paragraph further states that in response to this, numerous vitamins and preparations containing essential elements are sold as geriatric preparations,

and a preparation which makes possible the simple and efficient administration of these trace elements would be desirable.

There is no mention in this discussion regarding the administration of cadmium. The only reference to cadmium is in the title of one of the papers cited as authority for the statement that the absorption of zinc and copper decreases with age. To support this statement, the patentees cited M. Anke and H.J. Schneider, "Zinc, Cadmium and Copper Metabolism in Men;" *Arch. Exp. Veterinaermed.*, 25:805-809 (1971) (column 9, lines 27-29 of the '592 patent). Applicant has obtained a copy of this paper which is provided herewith, along with an English translation hereof, as Attachment A to this Amendment. As the examiner will note, this paper does not teach or suggest that cadmium should be administered to humans who are suffering from a cadmium deficiency. The paper simply reports, as the title of the paper indicates, on the metabolism of zinc, cadmium and copper in humans. The authors looked at differences in metabolism between men and women and at the effects of age on metabolism. In pertinent part, this paper provides that cadmium is stored in the liver and kidneys as people age, and that the kidneys of men have significantly more cadmium than the kidneys of women. The authors also reported that cadmium levels in kidneys for both men and women tended to decrease significantly

after the age of 70. They also found that there was variation in the concentration of zinc in kidneys and that this was determined by cadmium rather than by age. They stated (page 5 of the translation) that cadmium has a "metabolism-stressing" role and that their data showed the "toxic effects" of cadmium.

The authors further asserted that the kidneys and liver of persons who die from cardiac insufficiency, inflammatory pulmonary disease and malignant tumors contained a definitely established greater amount of cadmium; persons dying from infarction had a significantly lower concentration of cadmium than that of other patients. The authors asserted that cadmium may play a role in the occurrence of cardiac insufficiency, inflammatory pulmonary diseases and carcinoma. There is no suggestion that humans can suffer from a cadmium deficiency, much less that it would be desirable to treat such a deficiency by the administration of cadmium.

As noted above, the paper by Anke and Schneider is the only reference to cadmium in the '592 patent. The '592 patent, therefore, does not teach or suggest the presently claimed invention and does not anticipate claim 20 or 61.

Claims 20 and 61 also were rejected under 35 U.S.C. §102(b) as anticipated by U.S. Patent 5,130,298, issued to Cini et al. The examiner asserted that the '298 patent discloses that various

metals, including cadmium, can be administered to humans in a pharmaceutically acceptable cation salt or complex salt (citing column 3, line 64 - column 4, lines 7-9 and column 5), and that the disclosure inherently teaches treating a human suffering from a cadmium deficiency. This rejection is traversed.

The '298 patent teaches pharmaceutical compositions comprising human epidermal growth factor (EGF) and an amount of a pharmaceutically acceptable metal cation, such as zinc, sufficient to prevent the degradation of the EGF. The focus of the patent is on zinc as the metal cation. The patentees do note that other "suitable" cations "may" achieve the same effect (col. 3, lines 53-54). The patent goes on to state that a suitable cation "is one that is pharmaceutically acceptable, does not cause free radical formation and EGF degradation prevention properties and EGF biological activity maintaining properties" (col. 3, lines 64-68). The patent provides that "any monovalent, divalent or trivalent cation having such properties is within the scope of the present invention" (col. 4, line 1-2). The patentees then note that lanthanum forms a crystalline precipitate with EGF and that manganese, copper, iron and cobalt are not suitable because they cause free radical formation. They

then state that certain other cations, including cadmium, "may be suitable" (emphasis added; col. 4, lines 6-8).

The clear implication from this last statement, taken in context with those that preceded it, is that cadmium and the other cations listed with it (calcium, nickel, tin potassium and lithium) have not yet been tried and that the patentees do not know if they will be suitable or not. This is wholly inadequate to constitute a teaching of the administration of cadmium.

Furthermore, as noted above, the real focus of the '298 patent is the administration of EGF, principally topically for the healing of wounds. The patent provides that the EGF is provided as an aqueous solution having a concentration of about 250 µg/ml and that the zinc cation is provided at a concentration of about 10-20 mM. There is no teaching of what concentrations of other cations, should one be useful in place of the zinc, would be desirable.

Thus, this reference does not teach the administration of cadmium to persons who suffer from a cadmium deficiency, and certainly does not teach or suggest the administration of 0.025 - 2 mg of cadmium daily to minimize or eliminate a cadmium deficiency. This reference thus does not anticipate claims 20 or claim 61 of the present application.

Claims 21-22 and 25 were rejected under 35 U.S.C. § 103(a) as being obvious over the teachings of the Jacobson et al. paper or the '592 patent. The examiner stated that the references do not disclose the "particular unbalance levels of cadmium" in humans or the particular cadmium salt to be administered. She asserted, however, that it would have been obvious, to determine the level of cadmium and the particular salt to be administered so as to increase the concentration of cadmium in body fluids and tissues and correct a cadmium imbalance. This rejection is traversed.

The deficiencies of both the Jacobson et al. paper and the '592 patent have been discussed at length above, and those discussions are equally applicable to this rejection. The '592 patent does not teach the administration of cadmium at any concentration for any purpose, and the Jacobson et al. paper discloses the administration of small amounts of cadmium over a very short time period (five days). There is no indication that the persons to whom Jacobson et al. administered the cadmium (and other trace elements) were cadmium deficient, and the amounts of cadmium administered were not sufficient to treat a cadmium deficiency. Neither of these references renders obvious the invention of claims 21, 22 or 25.

Applicant respectfully submits that in view of the amendments and arguments presented herein, the invention claimed in the present application is in condition for allowance.

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Name	Barbara G. Ernst, Reg. No. 30,377				
Signature	Barbara G. Ernst			*Date*	June 16, 2004
Address	Rothwell, Figg, Ernst & Manbeck Suite 800, 1425 K Street, N.W.				
City	Washington	*State*	D.C.	*Zip Code*	20005
Country	U.S.A.	*Telephone*	202-783-6040	*Fax*	202-783-6031

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The presently claimed invention is directed to a method of treating a person suffering from deficient levels of cadmium in his body fluids and tissues by administering to the person a series of daily doses of cadmium at dose levels of about 0.025 mg to about 2 mg per day (equivalent to a dose level of about 25 - 2000 µg per day). This invention is not taught or suggested by Jacobson et al.

Jacobson et al. report a 5 day study in which they administered a number of trace elements parenterally to four

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Department of Animal Production and Veterinary Medicine of the Karl Marx University Leipzig
Animal Nutrition Section, Jena Region
(A. Hennig, Ph.D.)
and Urological University Hospital of the Friedrich Schiller University Jena
(Director: E. Hienzsch, Ph.D.)

Zinc, Cadmium, and Copper Metabolism in Man

By

M. Anke and H.-J. Schneider

with 5 Figures

(Received on March 26, 1971)

It has been demonstrated in experiments with various animal species that high dosages of cadmium cause significant deficiency phenomena and have a negative effect on growth, propagation efficiency, and life expectancy. No such high consumption is to be expected in man, although one cigarette contains somewhat more than 1 μg of cadmium, 70 percent of which appears in the smoke and may be deposited in the body (Nandi et al., 1969).

On the other hand man, because of his long lifetime in comparison to animal species, is subjected to significantly longer periods of cadmium absorption by way of foods, some of which contain substantial amounts of cadmium, as is demonstrated by the initial data of Kropf and Geldmacher-v. Mallinckrodt (1968).

Since systematic studies of the cadmium contained in man as a function of sex and age have not been available up to this point, the cadmium, copper, and zinc content, along with that of other components, of the liver, kidneys, rib, and prostate of 220 persons ranging in age from 0 to 90 years was studied. Ten samples each of males and females in the age groups of 0-1, 1-5, 6-10, and the following decades were analyzed.

Influence of Gender

A review of the study material as a whole indicates that gender definitely has an effect on the concentration of the elements zinc, cadmium, and copper (Table 1).

Table 1
Mean zinc, copper, and cadmium content of the liver, kidneys, and ribs of 220 persons 0-90 years of age

Elements	Liver		Kidneys		Ribs	
	E	Г	E	Г	E	Г
Zn (ppm)	304	248^{+++}	173	174^{-}	111	102^{+}
Cu (ppm)	35	27^{+++}	13	12^{-}	7.5	6.8^{-}
Cd (ppm)	3.64	4.37^{+}	29	44^{+++}	-	-

$^{+} = \alpha < 0.05$ $^{-} = \alpha > 0.05$

The liver of women contained significantly more zinc and copper, and that of men more cadmium. The most striking difference between the sexes is to be found in the cadmium content of the kidney. The kidneys of the male contained on the average 50 percent more cadmium than did those of the female. On the other hand, there was no difference between the sexes in the zinc and copper content of the kidneys. A definitely established difference in the zinc component of the ribs was observed for women; this difference is illustrated in Figure 1. The difference between the sexes from age 20 to age 30 and at the end of life is especially striking. The zinc content of the liver fully parallels the zinc content of the ribs.

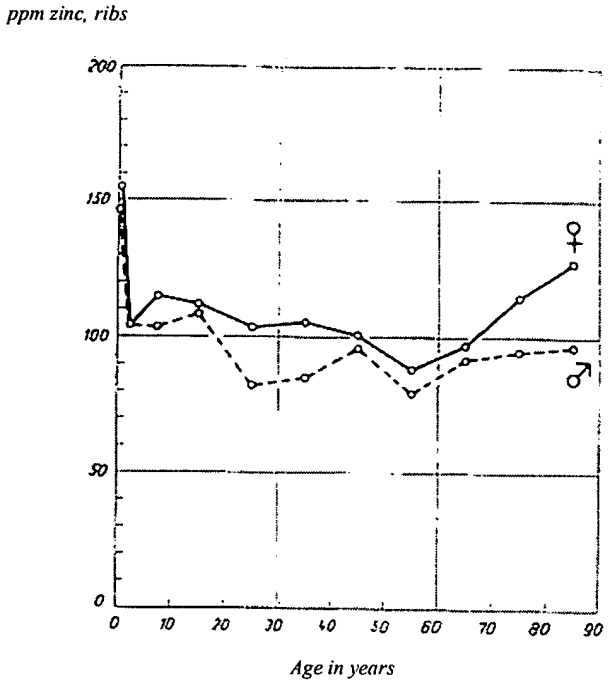

Figure 1. The zinc content of the fourth rib of man as a function of sex and age.

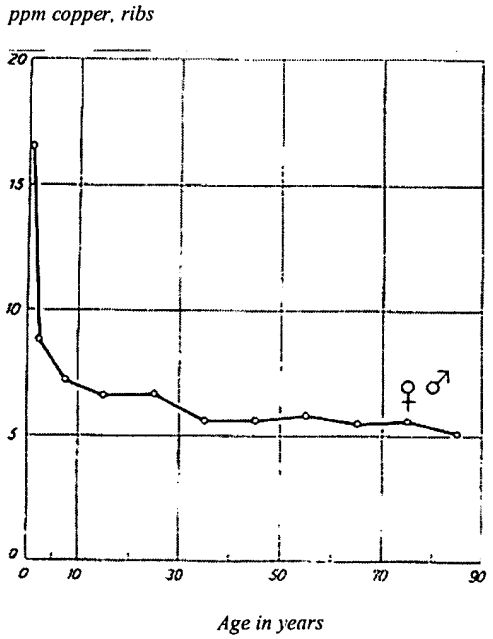

Fig. 2. The copper content of the fourth rib of man as a function of age.

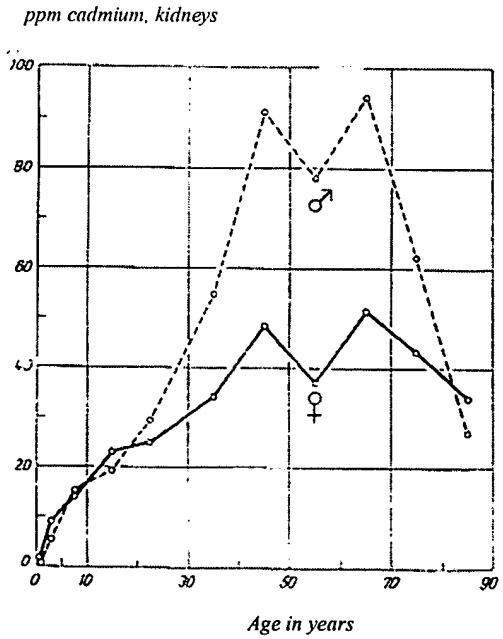

Fig. 3. The cadmium content of the kidneys of man as a function of age and sex.

The influence of age

In addition to the sex, the zinc, copper, and cadmium content of all organs studied exerts a highly significant influence.

The percentage of copper in the organs analyzed varies over the individual decades in a manner similar to the copper concentration of the rib (Figure 2). An extremely sharp drop in the first year of life was followed by gradual decrease to the end of life.

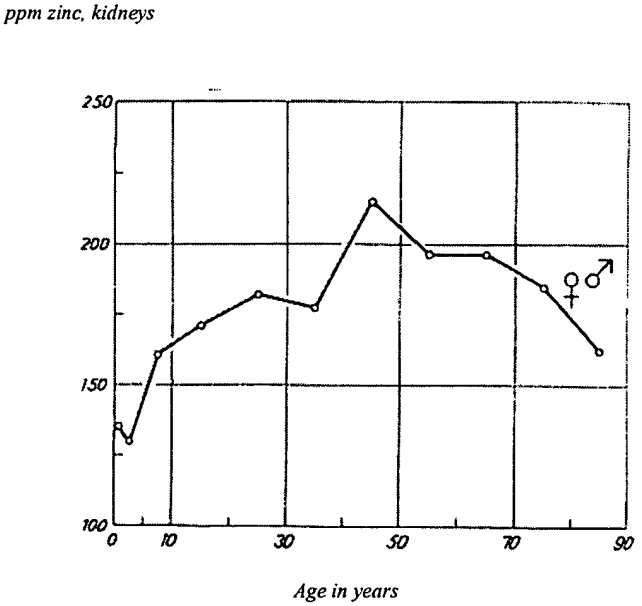

Fig. 4. The zinc content of the kidneys of man as a function of age

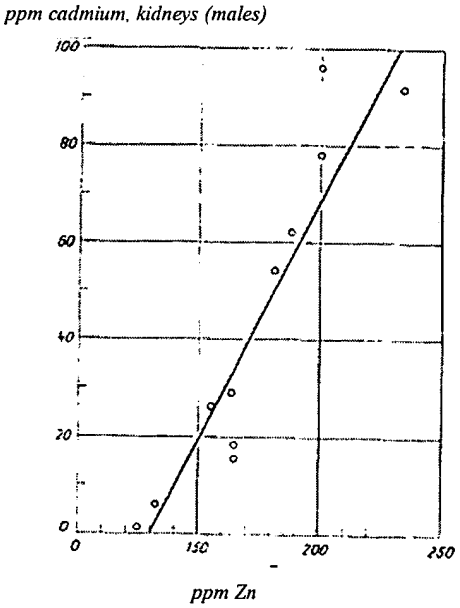

Fig. 5. Relationship of zinc content to cadmium content of the kidneys (y = 130.2 + 0.999 x)

The most striking influence of age is found in the case of cadmium. Children are virtually free of cadmium when born. Cadmium accumulates continually (Figure 3) both in the liver and in the kidneys according to the individual findings of Schroeder and Balassa (1961). The highest cadmium concentration in the body is stored in the kidneys. The difference in sex, with higher

values for the male, was manifested between the ages of 20 and 70. Examination of the trace of the curve reveals in particular increase in the cadmium content to just below 100 parts per million. It appears to be that persons dying at an advanced age of 70 to 90 have at age 50 a lower cadmium content than do persons dying at age 50.

The influence of age appeared to be expressed the most distinctly in the kidneys in the case of zinc (Figure 4). It increased continuously up to the age of 45 and then gradually decreased. In the other parts of the body it increased slowly from the first to the last decade. The variation in concentration of zinc in the kidneys is atypical and is determined by the cadmium concentration of the kidneys. This trace of the curve is accordingly determined by cadmium rather than by age. In other animal experiments conducted in our working group the addition of cadmium to feed and storage of cadmium also resulted in increased zinc storage. Zinc apparently exerts a protective effect. In the study material available to us the zinc content of the kidneys and cadmium percentage in males is positively correlated with a degree of certainty of 0.85 and in females with a degree of 0.61 (Figure 5).

This finding demonstrates the metabolism-stressing role of cadmium and indicates the toxic effects of this element. The cadmium accumulations in the kidneys of man are reached only in approximation in any animal organ studied without amounts of cadmium in the form of a salt. A maximum of 30 parts per million of cadmium was found in the kidneys of cattle.

Cadmium, zinc, and copper content of kidneys and liver in the presence of various diseases

It appeared to be of interest to devote greater study to the cadmium, zinc, and copper concentration of persons who had died of various diseases. Exitus due to cardiac infarction, cardiac insufficiency, inflammatory pulmonary affections, and carcinoma were selected and evaluated (Table 2). The age of the deceased ranged from 50 to 90 years. The effect of age is small over this period. Males and females were evaluated separately. The results for the sexes coincide. Only the content

percentages for males are presented; the figures in parenthesis indicate the number of cases investigated.

Table 2
Cadmium, zinc, and copper content of male kidneys and liver
at age 50 to 90 in the presence of various illness

Organs		Infarction (9) [1)]	Cardiac insufficiency (9)	Inflammatory pulmonary diseases (10)	Carcinoma (28)
Kidneys	Cd (ppm)	34	96	99	71
	Zn (ppm)	142	201	245	229
	Cu (ppm)	9.6	10.2	11.4	11.5
Liver	Cd (ppm)	4.4	7.4	7.2	6.6
	Zn (ppm)	232	209	318	298
	Cu (ppm)	15	22	27	24

1) Number of persons examined

The cadmium concentration of the kidneys and the liver of patients dying from infarction is significantly lower than that of other patients. It coincides with the percentage of content of persons dying from accidents. On the other hand, the kidneys and liver of the various persons perishing from cardiac insufficiency, inflammatory pulmonary diseases, and malignant tumors contained a definitely established greater amount of cadmium.

The zinc content of the organs follows the positive correlation between cadmium and zinc (Figure 5). The percentage of copper in the kidneys remained unaffected by the diseases. The differences involved in the liver could not be definitively established by biostatistical means.

The specific changes observed indicate that cadmium may play a role in the occurrence of cardiac insufficiency, inflammatory pulmonary diseases, and carcinomata. Cases of emphysema

found in workers who must come in contact with cadmium compounds have already been described in the case of pneumonia (Friberg, 1950; Bonell, 1955). The carcinoma of those who died of this disease was not localized in the kidneys and liver, so that the changes in metabolism due to cancer become evident. Cadmium accumulation associated with a higher percentage of zinc and copper, on the other hand, was observed in the organs examined.

Kippling and Waterhouse (1957) reported the occurrence of cancer of the prostate in workers who came in contact with cadmium dioxide. Kendrey and Roe (1969) made reference to sporadic occurrence of tumors and sarcomata in experimental animals subjected to the stress of cadmium. It appears that this aspect of the relationships determined should also be considered.

Summary

Zinc, cadmium and copper metabolism in man

There was a pronounced sexual dimorphism in tissue concentrations of zinc and cadmium: female organs contained more zinc than male organs, while the reverse applied to cadmium.

Age affected zinc, copper, and cadmium concentrations equally. The copper content or organs increased from birth until death, rapidly at first and then slowly. Cadmium increased continuously; kidney concentrations of 100 ppm or more, considered to be toxic, were encountered. In persons that had died from accident or from cardiac infarction the cadmium content of kidney was about 30 ppm, while in those who had died from inflammatory diseases of the lungs and malignant neoplasms the content was 75-100 ppm.

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Author: Manfred Anke, Ph.D., 69 Jena, Dornburger Strasse 24, and Hans-Joachim Schneider, Urological University Hospital of the Friedrich Schiller University Jena, 69 Jena, Lessingstrasse 1.

Sektion Tierproduktion und Veterinärmedizin der Karl-Marx-Universität Leipzig
Fachgruppe Tierernährung, Bereich Jena
(Prof. Dr. habil. A. Kennig)
und Urologische Klinik der Friedrich-Schiller-Universität Jena
(Direktor: Prof. Dr. E. Mienzsch)

Der Zink-, Kadmium- und Kupferstoffwechsel des Menschen

von

M. Anke und H.-J. Schneider

Mit 5 Abbildungen

(Eingegangen am 26. März 1971)

In Cd-Versuchen mit verschiedenen Tierarten konnte nachgewiesen werden, daß hohe Cd-Gaben erhebliche Ausfallerscheinungen verursachen und Wachstum, Fortpflanzungsleistung und Lebenserwartung negativ beeinflussen. Beim Menschen ist kein derartig hoher Cd-Konsum zu erwarten, obwohl eine Zigarette etwas mehr als 1 µg Cd enthält, von dem 70% im Rauch erscheinen und im Körper eingelagert werden können (Nandi et al., 1969).

Andererseits ist der Mensch auf Grund seines im Vergleich zu den Tierarten langen Lebens wesentlich größeren Zeiträumen der Cd-Aufnahme über die Nahrungsmittel ausgesetzt, von denen einige, wie die ersten Erhebungen von Kropf und Geldmacher-v. Mallinckrodt (1968) zeigen, beträchtliche Cd-Mengen enthalten.

Da bisher keine systematischen Untersuchungen über den Cd-Gehalt des Menschen in Abhängigkeit von Geschlecht und Alter vorlagen, wurde der Cd-, Cu- und Zn-Gehalt neben anderen Komponenten bei 220 Personen im Alter von 0–90 Jahren in Leber, Nieren, Rippe und Prostata untersucht. In den Altersklassen von 0–1, 1–5, 6–10 und den folgenden Dezennien kamen jeweils 10 Proben von Männern und Frauen zur Analyse.

Der Einfluß des Geschlechtes

Das Geschlecht beeinflußt gesichert die Konzentration der Elemente Zn, Cd und Cu, wenn man das gesamte Untersuchungsmaterial betrachtet (Tab. 1).

Tabelle 1
Der mittlere Zink-, Kupfer- und Kadmiumgehalt der Leber, Nieren und Rippen von 220 Menschen im Alter von 0–90 Jahren

Elemente	Leber ♀	Leber ♂	Nieren ♀	Nieren ♂	Rippen ♀	Rippen ♂
Zn (ppm)	304	248^{+++}	173	174^{-}	111	102^{+}
Cu (ppm)	35	27^{+++}	13	12^{-}	7,5	$6,8^{-}$
Cd (ppm)	3,64	$4,37^{+}$	29	44^{+++}	–	–

$^{+} = \alpha < 0{,}05$ $^{-} = \alpha > 0{,}05$

Die Leber der Frauen enthielt signifikant mehr Zn und Cu, die des Mannes mehr Cd. Am auffälligsten ist der Geschlechtsunterschied im Cd-Gehalt der Nieren. Die Nieren des Mannes besaßen im Mittel 50% mehr Cd als die der Frau. Demgegenüber ergab sich keine Geschlechtsdifferenz im Zn- und Cu-Gehalt der Nieren. Im Zn-Anteil der Rippen zeigte sich eine gesicherte Differenz zugunsten der Frau, die in der Abbildung 1 dargestellt wird. Der Geschlechtsunterschied zwischen 20 und 30 Jahren und am Lebensende fällt besonders ins Auge. Der Zn-Gehalt der Leber verläuft völlig parallel zu dem Zn-Gehalt der Rippen.

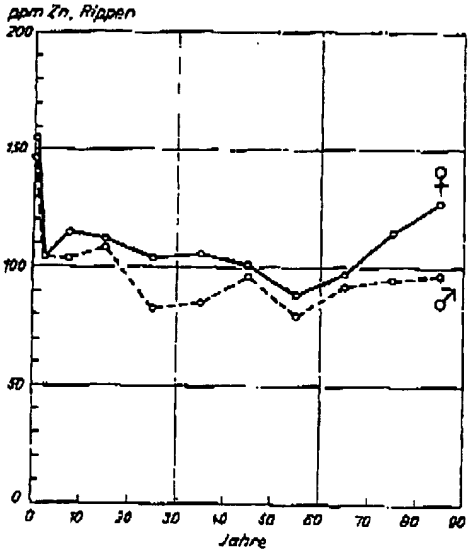

Abb. 1. Der Zn-Gehalt der 4. Rippe des Menschen in Abhängigkeit von Geschlecht und Alter

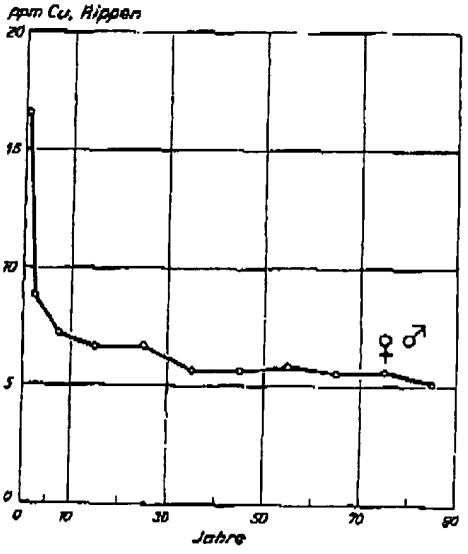

Abb. 2. Der Cu-Gehalt der 4. Rippe des Menschen in Abhängigkeit vom Alter

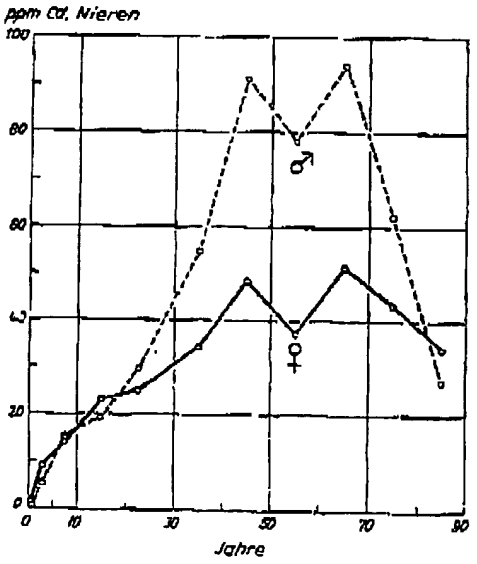

Abb. 3. Der Cd-Gehalt der Nieren des Menschen in Abhängigkeit von Alter und Geschlecht

Der Einfluß des Alters

Neben dem Geschlecht beeinflußt auch das Alter den Zn-, Cu- und Cd-Gehalt aller untersuchten Organe hochsignifikant.

Der Cu-Anteil der analysierten Organe verändert sich im Lauf der einzelnen Dezennien ähnlich der Cu-Konzentration der Rippe (Abb. 2). Einem außerordentlich starken Abfall im ersten Lebensjahr folgte ein allmählicher Rückgang bis zum Lebensende.

Am auffälligsten ist der Alterseinfluß beim Cd. Die Kinder werden praktisch Cd-frei geboren. Sowohl in der Leber als auch in den Nieren reichert sich das Cd in Übereinstimmung mit den Einzelbefunden von Schröder und Balassa (1961) kontinuierlich an (Abb. 3). In den Nieren wird die höchste Cd-Konzentration des Körpers gespeichert. Die Geschlechtsdifferenz mit höheren Werten für den Mann manifestierte sich zwischen 20 und 70 Jahren. Bei Betrachtung des Kurvenverlaufes fällt der Anstieg des Cd-Gehaltes der Nieren bis knapp 100 ppm besonders auf. Es scheint so zu sein, daß die im höheren Alter von 70–90 Jahren Verstorbenen, mit 50 Jahren einen niedrigeren Cd-Anteil in den Nieren besitzen als die mit 50 Jahren Verschiedenen.

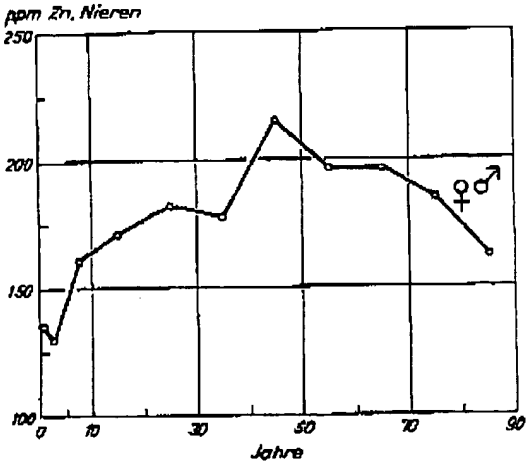

Abb. 4. Der Zn-Gehalt der Nieren des Menschen in Abhängigkeit vom Alter

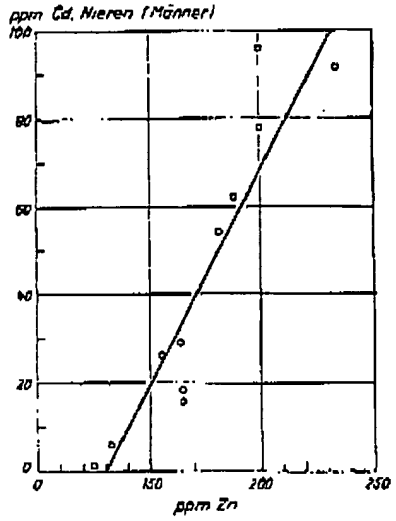

Abb. 5. Die Beziehung zwischen dem Zn- und Cd-Gehalt der Nieren ($y = 130{,}3 + 0{,}969\,x$)

Der Alterseinfluß zeigte sich beim Zn scheinbar in den Nieren am deutlichsten (Abb. 4). Er stieg bis zum Alter von 45 Jahren kontinuierlich an, um sich dann wieder allmählich zu verringern. In den anderen Körperteilen erhöhte er sich langsam vom ersten bis letzten Dezennium. Der Konzentrationsverlauf ist für das Zn in den Nieren atypisch und wird durch die Cd-Konzentration der Nieren bestimmt. Dieser Kurvenverlauf ist demnach nicht alters-, sondern Cd-bedingt. Bei anderen, in unserem Arbeitskreis durchgeführten Tierversuchen führte die Cd-Beifütterung und -speicherung immer auch zu einer verstärkten Zn-Einlagerung. Das Zn übt offensichtlich eine Schutzwirkung aus. In dem uns zur Verfügung stehenden Untersuchungsgut war der Zn-Gehalt der Nieren und der Cd-Anteil bei den Männern mit einem Bestimmtheitsmaß von 0,85 und den Frauen von 0,61 positiv korreliert (Abb. 5).

Dieser Befund demonstriert die stoffwechselbelastende Rolle des Cd und verweist auf die toxischen Einflüsse dieses Elements. Die Cd-Anhäufungen in den Nieren des Menschen werden von keinem untersuchten Tierorgan ohne Cd-Gaben in Salzform auch nur annähernd erreicht. In den Rindernieren wurden höchstens 30 ppm Cd ermittelt.

Der Kadmium-, Zink- und Kupfergehalt von Nieren und Leber bei verschiedenen Krankheiten

Es lag nahe die Cd-, Zn- und Cu-Konzentration der Organe von Personen, die an verschiedenen Krankheiten verstorben sind, näher zu untersuchen. Dabei wurden Exitus an Herzinfarkt, Herzinsuffizienz, entzündlichen Lungenerkrankungen und Karzinom ausgewählt und ausgewertet (Tab. 2). Die Verstorbenen hatten ein Alter von 50–90 Jahren. In diesem Zeitraum ist der Alterseinfluß klein. Männer und Frauen wurden getrennt ausgewertet. Die Ergebnisse stimmen bei den Geschlechtern überein. In der Tabelle 2 sind nur die Gehaltszahlen von Männern dargestellt, wobei die Zahlen in den Klammern die Zahl der untersuchten Fälle angeben.

Tabelle 2
Der Kadmium-, Zink- und Kupfergehalt von Nieren und Leber bei verschiedenen Krankheiten des Mannes im Alter von 50–90 Jahren

Organe		Infarkt (9)[1])	Herzinsuffizienz (9)	Entzündliche Lungenerkrankungen (10)	Karzinom (28)
Nieren	Cd (ppm)	34	96	99	71
	Zn (ppm)	142	201	246	229
	Cu (ppm)	9,6	10,2	11,4	11,5
Leber	Cd (ppm)	4.4	7,4	7,2	6,6
	Zn (ppm)	232	209	318	298
	Cu (ppm)	15	22	27	24

[1]) Anzahl der untersuchten Personen

Die Cd-Konzentration der Nieren und der Leber Infarktverstorbener ist signifikant niedriger als die der anderen Kranken. Sie deckt sich mit den Gehaltszahlen bei Unfallverstorbenen. Demgegenüber enthielten Nieren und Leber der an Herzschwäche, entzündlichen Lungenerkrankungen und bösartigen Tumoren Verschiedenen gesichert mehr Cd.

Der Zn-Gehalt der Organe folgt der positiven Korrelation zwischen Cd und Zn (Abb. 5). Der Cu-Anteil der Nieren blieb durch die Krankheiten unbeeinflußt. In der Leber ließen sich die gegebenen Differenzen biostatistisch nicht sichern.

Die gefundenen gerichteten Veränderungen deuten an, daß das Cd möglicherweise eine Rolle bei dem Auftreten von Herzinsuffizienz, entzündlichen Lungenerkrankungen und Karzinomen spielt. Im Fall der Pneumonie sind Cd-bedingte Emphyseme bei Arbeitern, die mit Cd-Verbindungen umgehen müssen, beschrieben (Friberg, 1950; Bonell, 1955). Bei den Karzinomverstorbenen war das Karzinom nicht an Nieren und Leber lokalisiert, so daß die krebsbedingten Veränderungen im Stoffwechsel sichtbar werden. Wiederum zeigt sich eine Cd-Anreicherung, verbunden mit einem vermehrten Zn- und Cu-Anteil, in den untersuchten Organen.

Kipping und Waterhouse (1967) berichteten über das Auftreten von Prostatakarzinomen bei Arbeitern, die mit CdO_2 umgehen. Kendrey und Roe (1969) verwiesen auf sporadisches Vorkommen von Tumoren und Sarkomen bei Cd-belasteten Versuchstieren. Es scheint, daß die gefundenen Abhängigkeiten auch unter diesem Aspekt zu sehen sind.

Zusammenfassung

Für die Elemente Zn und Cd besteht ein ausgeprägter Geschlechtsdimorphismus beim Menschen. Die Organe der Frau sind Zn-, die des Mannes Cd-reicher.

Das Alter beeinflußt die Zn-, Cu- und Cd-Konzentration gleichfalls. Der Cu-Gehalt der Organe nimmt von der Geburt bis zum Lebensende zunächst sehr rasch und dann lang-

sam ab. Der Cd-Anteil steigt demgegenüber kontinuierlich an und erreicht bei 100 ppm in der Niere lebensbedrohende Werte. Bei Unfall- und Herzinfarktverstorbenen betrug die Cd-Konzentration der Nieren 30 ppm; an Herzinsuffizienz, entzündlicher Lungenerkrankung und bösartigen Tumoren Verstorbene hatten 75–100 ppm in den Nieren.

Резюме

Обмен цинка, кадмия и меди у человека

Содержание элементов Zn и Cd у человека имеет выраженный половой диморфизм. Органы женщины более богаты цинком, органы мужчин-кадмием.

Возраст также оказывает влияние на концентрацию цинка, меди и кадмия. Содержание меди уменьшается с момента рождения до конца жизни сначала очень быстро, а затем – более постепенно. Содержание кадмия, в противоположность к этому, постепенно повышается и достигает при 100 ppm в почках количества, опасного для жизни. У умерших в результате травмы и инфаркта миокарда концентрация кадмия в почках составляла 30 ppm, у умерших от сердечной недостаточности, воспалений легких и злокачественных опухолей концентрация кадмия в почках составляла от 75 до 100 ppm.

Summary

Zinc, cadmium and copper metabolism in man

There was a pronounced sexual dimorphism in tissue concentrations of Zn and Cd: female organs contained more Zn than male organs, while the reverse applied to Cd.

Age affected Zn, Cu and Cd concentrations equally. The Cu content of organs increased from birth until death, rapidly at first and then slowly. Cadmium increased continuously; kidney concentrations of 100 ppm or more, considered to be toxic, were encountered. In persons that had died from accident or from cardiac infarction the Cd content of kidney was about 30 ppm, while in those who had died from inflammatory diseases of the lungs and malignant neoplasms the content was 75–100 ppm.

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Verfasser: Doz. Dr. habil. Manfred Anke, 69 Jena, Dornburger Straße 24, und Doz. Dr. sc. Hans-Joachim Schneider, Urologische Klinik der Friedrich-Schiller-Universität Jena, 69 Jena, Lessingstraße 1.